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10/552,494	08/01/2006	Yves St-Denis	PB60162B	2332

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EXAMINER	
JAISLE, CECILIA M	
ART UNIT	**PAPER NUMBER**
1624	

NOTIFICATION DATE	DELIVERY MODE
11/02/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/552,494	ST-DENIS, YVES	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 10-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 10-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-07-2005 and 11-07-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Priority

Applicants claim for priority based on US Prov. Appln. No. 60485322 is noted. However, the disclosure of US Prov. Appln. No. 60485322 is more limited than the present application's disclosure. Accordingly, this application is entitled to the priority date of US Prov. Appln. No. 60485322 only for the subject matter supported thereby.

Lack of Unity

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions that are not so linked as to form a single general inventive concept under PCT Rule 13.1.
In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 1-3 and 10-13, drawn to compounds of Formula I, wherein X and Y are each carbon, classified in class 544, subclasses 8, 238, 315 and 405, and class 546, subclasses 157, 159, 160 and 167, pharmaceutical compositions thereof and therapeutic methods using these compounds, classified in class 514, subclasses 222.5, 252.04, 255.05, 269, 312, 313 and 314.

II. Claims 1-4 and 10-13, drawn to Formula I compounds, where X is carbon and Y is nitrogen, classified in class 544, subclasses 8 and 284, pharmaceutical

compositions and therapeutic methods using these compounds, classified in class 514, subclasses 222.5, 252.02, 255.05, 266.21, 266.23 and 266.1.

III. Claims 1-4 and 10-13, drawn to compounds of Formula I, wherein X is nitrogen and Y is –CR7, classified in class 544, subclasses 8, 238, 315 and 405, class 546, subclasses 157, 159, 160 and 167, pharmaceutical compositions and therapeutic methods using these compounds, classified in class 514, subclasses 222.5, 252.04, 255.05, 269, 312, 313 and 314.

IV. Claims 1-5 and 10-13, drawn to Formula I compounds, where X and Y are both nitrogen and a process for preparing them, classified in class 544, subclasses 8, 238 and 279, pharmaceutical compositions and therapeutic methods using these compounds, classified in class 514, subclasses 222.5, 252.04, 255.05 and 269.

Each group set forth above lacks unity with each other group, i.e., there is no single general inventive concept. The unique special technical features in each group are the identities of the four patentably distinct X- and Y-containing bicyclic ring systems of Formula I. The technical relationship among the inventions does not involve at least one common or corresponding special technical feature. The expression "special technical feature" is defined to mean those technical features that define the contribution each claimed invention, considered as a whole, makes over the prior art. In this case, a reference that could be used to reject compounds of Formula I of Group I could not be used to reject compounds of Formula I of Groups II - IV.

The Group I invention has special technical features not common to Groups II - IV and would be expected to be useful other than as disclosed, e.g., as intermediates to

agricultural insecticides (US 20070203181). Also, the Group II invention has special technical features not common to Groups I, III and IV and would be expected also to be useful as antiproliferative agents (US 20070149546). The Group III invention has special technical features not common to Groups I, II and IV and would be expected to be useful as intermediates to antiviral agents (US 20070185121).

During a telephone conversation with Ms. Laura K. Madden on Oct. 4, 2007, a provisional election was made with traverse to prosecute the invention Group IV, claims 1-5 and 10-13. Applicant must affirm this election in reply to this Office action. Claims 1-5 and 10-13 are under examination only to the extent that they are directed to the elected subject matter. Otherwise, the non-elected subject matter of claims 1-5 and 10-13 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b).

To preserve a right to petition, the reply to this Office Action must distinctly and specifically point out supposed errors in the restriction requirement, or the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for CFR binding activity *in vitro* and CFR functional assay *in vitro*, does not reasonably provide enablement for treatment of any condition mediated by CFR (claim 11), or where the condition is depression or anxiety (claim 12), or IBS or IBD (claim 13). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed scope includes unnamed conditions mediated by CFR for which there is no enabling disclosure. The compounds are disclosed to be *in vitro* inhibitors of CRF and the specification recites that the compounds are therefore useful to treat all conditions mediated by CRF, for which the specification provides no competent evidence. Furthermore, the specification does not provide competent evidence that the instantly disclosed tests are predictive of all uses disclosed and embraced by the claims for the intended host.

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq.* This application's disclosure is insufficient to enable the instantly claimed methods based solely on *in vitro* inhibition of CRF activity. The state of the art indicates the requirement for undue experimentation.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013

(Fed.Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

(1) Breadth of claims.

(a) Scope of the compounds. The claims cover potentially billions of pyrido-pyrimidines of Formula (I).

(b) Scope of the diseases and kinases covered. The scope of all the conditions said to be mediated by CRF, including depression, anxiety, IBS and IBD. The claims encompass all conditions, including ones yet to be determined, embraced by the term "condition mediated by CRF."

(2) The nature of the invention and predictability in the art: Therapeutic use of novel compounds in treating all conditions said to be mediated by CRF. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information is so meager, that it would require extensive experimentation to determine a specific dosage for a specific recited disease, mode of administration and therapeutic regimen. Moreover, the dosage is generic; the same for the many disorders covered by the specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for various types of conditions and diseases.

No dosage or therapeutic regimen is present to direct the skilled artisan to protect a potential host from all conditions mediated by CRF.

(4) State of the Prior Art: This record does not recognize any pyrimido-pyridines structurally related to the compounds of Formula (I) that have been used for the treatment of all of the conditions mentioned and construed as mediated by CRF.

Arborelius, et al., J. Endocrinol. (1999) 160, 1-12, reports only "the hypothesis that CRF receptor antagonists may represent a novel class of antidepressants and/or anxiolytics."

Zorrilla, et al., Brain Research 952 (2002) 188-199, also reports "the hypothesis that CRF antagonists may be useful for the pharmacotherapy of pathological anxiety."

Taché, et al., Brit. J. Pharmacol., (2004) 141, 1321-1330, suggests, "Targeting CRF1-dependent pathways may have potential benefit against stress or anxiety-/depression-related functional bowel disorders."

Hisamatsu, et al., J. Gastroenterol. 2007:42 [Suppl XVII]: 34-40, acknowledges, "both central and peripheral CRF systems are stimulated by stress and may have the potential to regulate gut homeostasis and so influence IBD phathophysiology." However, the authors caution, "further well-organized prospective studies using scientific methodology to measure psychological stress are necessary.'

The ability of a compound that inhibits CRF activity to treat all conditions is open to proof.

(5) Working Examples: No disclosure correlates *in vitro* results to *in vivo* prevention and treatment of all conditions associated with CRF activity or those conditions specifically named. The specification prophesies that the methods will treat all conditions associated with CRF activities, but no working examples actually show treatment of even a single condition specifically attributable to CRF activity.

The specification discloses that the compounds of formula (I) function by inhibiting all CRF activity associated with a debilitating condition, for which Applicants provide no competent evidence. Furthermore, Applicants have not provided competent evidence of known tests that are highly predictive for all CRF activity by the claim language for the intended host.

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present,

> "The first paragraph of 35 U.S.C. 112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."

Plant Genetic Systems N.V. v. DeKalb Genetics Corp., 65 USPQ2d 1452, 1456 (Fed.Cir. 2003). Also, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

(6) Skill of those in the art: See the detailed discussion above of Arborelius, Zorrilla, Taché and Hisamatsu. The state of the art supports that successful treatment of all conditions mediated by CRF is subject to further investigation.

(7) The quantity of experimentation needed: Based on the disclosure content, to use the invention would place an undue burden on one skilled in the pharmaceutical arts, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for the reasons stated above.

The discussion of the above factors demonstrates that the present application sufficiently lacks enablement of the present claims. In view of the breath of the claims, the pharmaceutical nature of the invention, the unpredictability of relationship between kinase activity and prevention and treatment of all diseases, one of ordinary skill in this art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states,

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed.Cir. 1993).

Claims 1-5 and 10-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutically acceptable salts and stereoisomers of the Formula I compounds, does not reasonably provide enablement for pharmaceutically acceptable solvates and prodrugs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims, insofar as they embrace solvates, are not enabled. The specification prophesizes solvates, but the numerous examples presented all failed to produce a

solvate. The evidence of the specification is clear: These compounds do not possess the property of forming solvates; there is no evidence that such solvates even exist.

A prodrug of a compound must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance *in vivo* at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria requires a clinical trial setting and a large quantity of experimentation. Finding a prodrug of the claimed compounds would be an empirical exercise. Predicting, for example, if a certain ester of an acid is in fact a prodrug that produces the active compound metabolically at a therapeutic concentration and a useful rate is filled with experimental uncertainty. Attempts have been made to predict drug metabolism *de novo*, but this is still an experimental science.

Thus, this is a circumstance where the "specification is evidence of its own inadequacy" (*In re Rainer*, 153 USPQ 802, 807). These derivatives cannot be simply willed into existence. *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 states:

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist ... the examples of the '881 patent do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The same circumstance appears true here: no evidence shows that solvates and prodrugs of these compounds actually exist; if they did, they would have formed. Applicants must show making solvates and prodrugs, or limit the claims accordingly.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 and 10-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1: The plural recitation of "A compound, including stereoisomers" reads on unsupported mixtures of the inventive compounds and should be singularized.

Claims 1-4 and 10-13: The recitation of "a prodrug" fails to define the parent compound from which the prodrug is intended to be formed.

Claim 5: The recitation of "a suitable amine," "a suitable protecting group," "a suitable oxidizing agent," "a suitable reducing agent," "a suitable leaving group," ans "the suitable reactive –Z-W derivative," fails to define the intended reaction when there is no definition of the conditions to which the recited reagent is to be "suitable." The recitation of "the usual conditions," fails to define the intended reaction when there is no definition of the conditions considered to be "suitable." The phrase "preferably chloride" renders the claim indefinite because it is unclear whether the preferred limitation is part of the claimed invention. See MPEP § 2173.05(d).

Objected Claims

Claims 1-5 and 10-13 are objected to as directed to both elected and non-elected subject matter. The claims should be amended to recite only elected subject matter.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cecilia M. Jaisle, J.D.
10/18/2007

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